

**EXAMINER'S AMENDMENT**

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Barry Wilson on 4/19/11.

The application has been amended as follows:

- Claim 1 (currently amended): A method of measuring the amount of an unlabeled organic acid in a biological sample, comprising:
  - a) adding to a biological sample suspected of containing the unlabeled organic acid to be measured an amount of a standard comprising one or more oxygen-18 labeled organic acids, wherein at least one of the oxygen-18 labeled organic acids belongs to an organic acid class selected from the group consisting of dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate, glyoxylic acid, hydroxyl mono-acid selected from the group consisting of glycolic acid, lactic acid, 3-hydroxypropionic acid, 2-hydroxybutyric acid, 3-hydroxyisobutyric acid, 3-hydroxybutyric acid, 4-hydroxybutyric acid, 2-hydroxyisovaleric acid, 3-hydroxy-2-methylbutyric acid, 3-hydroxyisovaleric acid, 3-hydroxy-2-ethylpropionic acid, 3-hydroxyvaleric acid, 4-hydroxyisovaleric acid, 5-hydroxyhexanoic acid, 2-hydroxyisocaproic acid, 2-hydroxy-3-methylvaleric acid, 5-hydroxyhexanoic acid, 3-hydroxy-2-methylvaleric acid, 2-hydroxyphenylacetic acid, 4-hydroxy phenylacetic acid, 4-hydroxycyclohexylacetic acid, phenyllactic acid, 4-hydroxyphenylpropionic acid, 5-hydroxyindoleacetic acid, indoleacetic acid and 3-hydroxydodecanoic acid, and keto acid, and wherein at least one of said oxygen-18 labeled organic acids is structurally similar or identical to the unlabeled organic acid to be measured;

- b) processing the sample to increase the concentration of and/or chemically modify the unlabeled organic acid to be measured;
- c) measuring the amount of unlabeled organic acid and oxygen-18 organic acid in the processed sample by mass spectrometry; and
- d) using the amount of oxygen-18 organic acid measured in step c) to adjust the measured amount of unlabeled organic acid measured in the processed sample so as to reflect the amount of unlabeled organic acid originally present in the sample.

- Claim 7 (currently amended): The method of claim 1 wherein said processing ~~results in an enrichment of~~ comprises increasing the concentration of the unlabeled organic acid in the sample.
- Claim 8 (currently amended): The method of claim 1, wherein said processing comprises chemically modifying results in chemical modification of the unlabeled organic acid in the sample.
- Claim 9 (currently amended): A method of measuring the amount of at least one unlabeled organic acid in a biological sample, comprising:
  - a) adding to a biological sample suspected of containing the at least one unlabeled organic acid to be measured an amount of oxygen-18 labeled organic acids, wherein the oxygen-18 labeled organic acids comprise at least one acid selected from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and keto acid;
  - b) processing the sample to increase the concentration of and/or chemically modify the unlabeled organic acid to be measured;
  - c) measuring the amount of unlabeled organic acids and oxygen-18 organic acids in the processed sample by mass spectrometry; and
  - d) using the amount of an oxygen-18 organic acid measured in step c) to adjust the measured amount of a structurally similar or identical unlabeled

organic acid ~~measured~~ in the processed sample so as to reflect the amount of unlabeled organic acid originally present in the sample.

- Claim 12 (currently amended): The method of claim 9 wherein said processing ~~results in an enrichment of~~ comprises increasing the concentration of the unlabeled organic acid in the sample.
- Claim 13 (currently amended): The method of claim 9 wherein said processing comprises chemically modifying results in chemical modification of the unlabeled organic acid in the sample.
- Claim 30 (Currently Amended) A method of diagnosing an individual with a metabolic defect characterized by an abnormal amount of an unlabeled organic acid in a biological sample of the individual, said method comprising:
  - a) adding to a biological sample from the individual an amount of a standard comprising one or more oxygen-18 labeled organic acids, wherein at least one of the oxygen-18 labeled organic acids belong to an organic acid class selected from the group consisting of dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate, glyoxylic acid, hydroxyl mono-acid selected from the group consisting of glycolic acid, lactic acid, 3-hydroxypropionic acid, 2-hydroxybutyric acid, 3-hydroxyisobutyric acid, 3-hydroxybutyric acid, 4-hydroxybutyric acid, 2-hydroxyisovaleric acid, 3-hydroxy-2-methylbutyric acid, 3-hydroxy isovaleric acid, 3-hydroxy-2-ethylpropionic acid, 3-hydroxyvaleric acid, 4-hydroxyisovaleric acid, 5-hydroxyhexanoic acid, 2-hydroxyisocaproic acid, 2-hydroxy-3-methylvaleric acid, 5-hydroxyhexanoic acid, 3-hydroxy-2-methylvaleric acid, 2-hydroxyphenylacetic acid, 4-hydroxy phenylacetic acid, 4-hydroxycyclohexylacetic acid, phenyllactic acid, 4-hydroxyphenylpropionic acid, 5-hydroxyindoleacetic acid, indoleacetic acid and 3-

hydroxydodecanoic acid, and keto acid, and wherein at least one oxygen-18 labeled organic acid is structurally similar or identical to the unlabeled organic acid to be measured;

- b) processing the sample to increase the concentration of and/or chemically modify the unlabeled organic acid to be measured;
- c) measuring the amount of unlabeled organic acid and oxygen-18 organic acid in the processed sample by mass spectrometry;
- d) using the amount of oxygen-18 organic acid measured in step c) to adjust the measured amount of unlabeled organic acid measured in the processed sample so as to reflect the amount of unlabeled organic acid originally present in the sample; and
- e) determining if the amount of the unlabeled organic acid detected in the sample is an abnormal amount, thereby diagnosing the existence a metabolic defect in the individual.

- Claim 31 (Currently Amended) The method of claim 30 wherein said processing ~~results in an enrichment of~~ comprises increasing the concentration of the unlabeled organic acid in the sample.
- Claim 32 (Currently Amended) The method of claim 30 wherein said processing comprises chemically modifying results in chemical modification of the unlabeled organic acid in the sample.
- Claim 37 (Currently Amended) A method of diagnosing an individual with a metabolic defect characterized by an abnormal amount of at least one unlabeled organic acid in a sample of the individual, said method comprising:
  - a) adding to a sample from the individual an amount of oxygen-18 labeled organic acids, wherein the oxygen-18 labeled organic acids comprise at least one acid selected from each of hydroxy mono-acid, dihydroxy mono-

acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate, and keto acid;

- b) processing the sample to increase the concentration of and/or chemically modify the unlabeled organic acid to be measured;
- c) measuring the amount of unlabeled organic acids and oxygen-18 organic acids in the processed sample by mass spectrometry;
- d) using the amount of an oxygen-18 organic acid measured in step c) to adjust the measured amount of a structurally similar or identical unlabeled organic acid measured in the processed sample so as to reflect the amount of the at least one unlabeled organic acid originally present in the sample; and
- e) determining if the amount of the at least one unlabeled organic acid originally present in the sample is an abnormal amount, thereby diagnosing the existence a metabolic defect in the individual.

- Claim 40 (Currently Amended) The method of claim 37 wherein said processing ~~results in an enrichment of~~ comprises increasing the concentration of the unlabeled organic acid in the sample.
- Claim 41 (Currently Amended) The method of claim 37 wherein said processing comprises chemically modifying results in chemical modification of the unlabeled organic acid in the sample.
- **Claim 57** is canceled.

***Allowable Subject Matter***

2. **Claims 1, 3, 4, 6-13, 15-17, 30-32, 34-41, 43-56 and 58-61** are allowed.
3. The following is an examiner's statement of reasons for allowance: Peterson et al. (*J. Lipid Research*, 1988, previously referenced) and Nguyen et al. (US 2005/0070023, previously referenced) are considered the closest prior art of record. Peterson discloses a method of labeling glycolic acid with oxygen-18 at the C-O-acyl

bond (see abstract). Nguyen discloses a method of using isotope labeled internal standards in analysis of carboxylic acids (abstract). However, neither of the references discloses a method of measuring an unlabeled organic acid set forth in the above claims. Specifically, the references do not disclose adding an amount of a standard comprising an oxygen-18 labeled organic acid as listed in the above claims to a biological sample or processing the sample to increase the concentration of or chemically modify the unlabeled acid to be measured. Further, the claims as amended overcome any 35 U.S.C. 112 issues and are supported by existing technical knowledge.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID WEISZ whose telephone number is (571)270-7073. The examiner can normally be reached on Monday - Thursday, 7:30 a.m. - 5:00 p.m., EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

4/21/2011  
/D. W./  
Examiner, Art Unit 1777

/Yelena G. Gakh, Ph.D./  
Primary Examiner, Art Unit 1777